Scars are held to a minimum of noticeability by suitable planning of the incision lines, and by placing all tension of approximation on the fascia instead of the skin.

REFERENCES

1. Plastic Reconstruction of the Anomalous Breast (Bames), Revue de Chirurgie Structive No. 2, June, 1936.
2. A Review of Plastic Operations on the Breast (Bames), Medical Record, April, 1936.

727 West Seventh Street.

DISCUSSION

JOHN HUNT SHEPHARD, M.D. (Medico-Dental Building, San Jose).—While enlarged breasts do not endanger life, they frequently do cause both physical and mental discomfort, entitling the patient to our earnest and sincere consideration.

For years these unfortunate individuals have had to choose between accepting the *status quo* or submitting to a mammectomy. Today we can offer them relief from their discomfort without partially desexing them, which, at times, does bring about serious psychological and domestic discord. Doctor Bames, by word and film, has shown us what he has been able to do for these patients, and he is to be congratulated upon his results.

My personal experiences with plastic operations on the breast is very limited; and while my results have not been as beautiful as Doctor Bames', my patients have been most grateful.

One point which Doctor Bames mentions in the technique of this operation I want to emphasize, namely, the preservation of the nerve and blood supply to the nipple and areola. The major blood supply to this area is quite superficial, and in the reflection of the superior flap one must keep his dissection close to the skin and do the most of it by a moist sponge over the fingers, instead of using a scalpel or scissors.

While the technique of this operation is not difficult, those of us who do not possess the eye of the sculptor will not be found exhibiting our results.

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NELSON J. HOWARD, M.D. (350 Post Street, San Francisco).—Count as fortunate those physicians who saw the colored motion pictures shown by Doctor Bames at the 1937 State meeting. No written description could convey half so well the operative technique or the cosmetic after-results as presented in this film.

It seems an unnecessary comment that only pathologically normal, distinctly enlarged or exceedingly pendulous breasts should be submitted to these operative procedures. Where one should draw the line between abnormally enlarged, or exceedingly pendulous breasts and normal pectoral protuberances, is the difficult thing to determine. In the minor grades of these abnormalities, especially in the distinctly pendulous breast, one can be surprised at the return of contours and more pleasing form which follow the prolonged wearing of modern types of uplift brassiers. This change is an anatomical one, the so-called suspensory ligaments of the breast shorten, and the subcutaneous fat of the upper border of the breast is no longer atrophic or gravitated dependent. With painful breasts, in which pain fails to be relieved by adequate support, one cannot expect pain to disappear by this operation. The sole purpose, then, of the operation is the cosmetic effect, which, however, can be obtained by effective modern brassiers, unless the hypertrophy of gland or fat tissue is extreme.

Any operative plastic procedure on the breast must preserve the nipple and areolar intact for physiological as well as psychological reasons. I should like to know whether Doctor Bames has encountered sloughing and necrosis of these structures in this operation. Again, it would be of interest to know how many of these patients have had subsequent pregnancies, and how many of them were able to nurse their babies.

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ARTHUR E. SMITH, M.D. (1930 Wilshire Boulevard, Los Angeles).—Plastic reconstruction of the enlarged breast has been done for many years with a varied degree of success by plastic surgeons in Europe. Inefficient surgical planning and procedure often resulted in the loss of nipples, asymmetry of the breasts, and excessive scarring and interference with normal glandular function. Therefore, plastic surgeons in the United States were reticent in accepting the surgical results of their European colleagues. One of the first reconstructive plastic procedures for mastopexy was suggested by Dartiques, who adjusted the breast tissue by axillary resection. Then, later, the perpendicular subareolar incision with the excision of superfluous glandular tissue was practiced which resulted in large disfiguring scars and asymmetry of breasts. Thorek, in 1922, described his surgical procedure, which was a great step forward in plastic reduction and consisted of making a supra-areolar curved incision over the pendulous mass, and a second curved incision just beneath the breast. Excessive adipose and glandular tissues between the two incisions were removed. The nipple and areolar tissues were separated from the surrounding skin by a circular incision. The surrounding skin was undermined and the reduced breast was pushed upward beneath the loosened skin. The nipple and areolar tissue emerged through a new opening at the desired location. By this technique the curved scar line was located beneath the breast.

For a number of years I have employed a two-stage technique in the plastic reconstruction of the enlarged breast. The primary stage is for the establishment of collateral circulation and consists of loosening the skin over the major portion of the breast. This diminishes the possibility of losing the nipple or skin by superficial necrosis at the time of the major reconstruction.

Two months later the second operation is done. One-half inch of skin outside the areolar tissue margin is included within the circular incision. The skin is de-epithelized to the skin-areolar tissue junction. Two convex incisions are made: the upper one over the breast, and the lower one in the curved outline beneath the breast. No vertical incisions are made. A disk of skin, the diameter of the areolar tissue only, is removed at normal breast level and nipple location. The skin over the entire breast is loosened and the circumference of the breast reduced; the newly molded breast is pushed upward, and the nipple and areolar tissues are advanced through the circular opening. The one-half inch of de-epithelized skin surrounding the areolar tissue is covered by the surrounding skin which gives greater skin surface contact and better blood supply. The only scar line is situated beneath and hidden by the overhanging breast.

I wish to emphasize that the greatest surgical exactitude is necessary in plastic reconstruction of pendulous, hypertrophied breasts in order to create proper contour, preserve glandular function, prevent surface necrosis and scarring, lumping, and asymmetry. Women in the social, theatrical, and business world, who possess excessively large breasts are subjected to a physical and psychic handicap, which can be overcome by proper surgical procedures.

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# SIMMONDS' DISEASE (HYPOPHYSEAL CACHEXIA)*

## CLINICAL REPORT OF SEVERAL CASES WITH DISCUSSION OF DIAGNOSIS AND TREATMENT

*By* ROBERTO F. ESCAMILLA, M.D.
AND
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*San Francisco*

DISCUSSION *by C. Kelly Canelo, M. D., San Jose; Lewis T. Bullock, M. D., Los Angeles.*

IN 1914, Simmonds,[1] a pathologist of Hamburg, first suggested that the symptom-complex, now recognized as hypophyseal cachexia, was due primarily to diminished function of the anterior hypophysis. He arrived at this conclusion after

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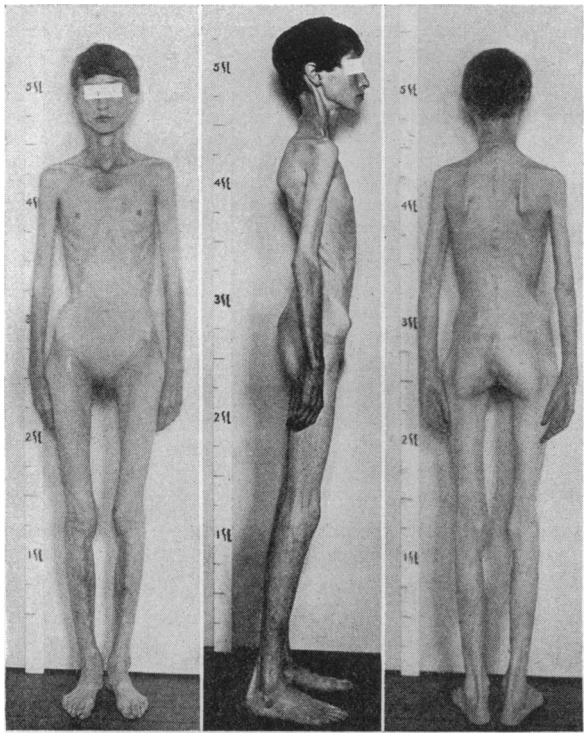

Fig. 1

several years of study of the structural changes in the pituitary gland in correlation with the clinical findings. As a result, the condition now known as Simmonds' disease has come to be generally recognized as a clinical entity.

Chief and most constant characteristics of the syndrome are: (1) marked loss of weight, frequently progressing to emaciation; (2) diminished sexual function; and (3) a very low basal metabolic rate. Other characteristic but less constant findings are: asthenia; intolerance to cold; premature senility; psychic changes; gastro-intestinal upsets; dry skin and hair, with loss of the latter particularly in the axillary and pubic regions; atrophy of the jaw-bone, and dental caries; low blood pressure; slow pulse rate; flat glucose tolerance curve with tendency to hypoglycemia (occasionally a diabetic type of curve); diminished specific dynamic reaction to food; secondary anemia; and visceromicria. The disease may occur in either sex at any age, but is most frequently found in females during those age periods when pituitary integrity is in greatest demand, as at puberty, during the menopause, or after many pregnancies.

Altogether, about 154 typical cases had been reported prior to 1936. However, as recently as 1933, Silver [2] accepted for his survey as cases of true Simmonds' disease only those in which necropsy findings had been reported—a total of forty-one cases at that time. The clinical picture now seems to be fairly well established, and is not likely to be confused with any other, with the possible exception of a state of severe malnutrition due to anorexia nervosa, of which amenorrhea may be a consequence.

We wish to present case histories of eight patients whose clinical findings, in our opinion, necessitate a diagnosis of Simmonds' disease, and one patient who was originally so classified but whose eventual course caused us to favor a diagnosis of anorexia nervosa. The fact that this number of cases has been collected in one clinic within a few years seems to indicate that the malady is not as rare as has been heretofore supposed. It is hoped that this presentation will stimulate consideration of the diagnosis of Simmonds' disease if cachexia is encountered that cannot be explained by any of the common causes.

## REPORT OF CASES*

CASE 1 (FIG. 1)—C. M. (43169M), a 25-year-old, single, Irish, female office worker, was admitted to the University of California Hospital on March 17, 1928, complaining of loss of weight and amenorrhea. In the past she had had the usual childhood diseases. It is of interest that one brother was thin. She had never menstruated.

When the patient was fifteen years of age she weighed 90 pounds (41 kilograms). At that time she had an attack of influenza, following which she began to lose weight rapidly and had associated symptoms of anorexia with slight constipation, and vomiting. A gastro-enterostomy was performed, resulting in some relief from vomiting. However, she continued to lose weight gradually, although she had occasionally slight temporary increase in weight during periods of rest and greater intake of food. Administration of ovarian and pituitary tablets did not improve her condition.

*Physical Examination.*—The patient's height was 62¾ inches (159 centimeters); her weight, 59¾ pounds (27 kilograms)—ideal weight, 124 pounds (56.3 kilograms). The pulse rate was 68 to 78 beats per minute, and the temperature was 36 to 37 degrees centigrade. She was emaciated. A downy growth of hair was present on the cheeks and upper lip, but elsewhere the hair was sparse and felt dry, especially in the axillary and pubic regions and outer thirds of the eyebrows. The jaw-bone was atrophied, but the teeth were in fair condition. The breasts were atrophic. Blood pressure was 88 millimeters of mercury systolic, and 64 diastolic. The finger nails were soft and ridged, and the tips of the fingers were cyanotic. Pelvic examination by Dr. Frank Lynch showed a small midline thickening which may have been a vestigeal uterus; and endoscopic examination revealed complete absence of the cervix.

*Laboratory Findings.*—Blood: hemoglobin, 78 per cent (12.2 grams) (Sahli); red blood cells 4,800,000 per cubic millimeter; white blood cells 9,000 per cubic millimeter, with a normal differential count, including 2 per cent eosinophils. Urine: faintest possible trace of albumin on one examination. Basal metabolic rate, 18.5 per cent minus. Blood sugar (fasting), 89 milligrams per cent. Roentgenological examination showed the sella turcica to be small and shallow; the bone age was that of an adult. Aschheim-Zondek and Allen Doisy folliculin tests on the urine, made in the laboratory of Dr. Herbert M. Evans, were negative. The blood was examined for anterior pituitary sex factors by Dr. C. Frederic Fluhmann of the Stanford Medical School, and these were not found.

*Course and Treatment.*—The patient was given anterior pituitary substance (Armour) in doses of five grains three times daily, with pancreatin. She improved slightly, but gained only 1¼ pounds in four months, at the end of which time the basal metabolic rate was 10.1 per cent minus. Eight months later she was found to have a diabetic type of glucose tolerance curve (blood sugar: fasting, 172; thirty-minute specimen lost; one hour 336; two hours 178 milligrams per cent; there were large amounts of sugar in the urine). One month later the curve had leveled somewhat as follows: fasting, 80; one-half hour 163; one hour 240; two hours 97 milligrams per cent. The patient was started on insulin therapy and a weighed diet of 1,620 calories. At this time her weight was 61 pounds (27.8 kilograms), and it gradually increased over a period of 10 months to 70 pounds (31.8 kilograms). The basal metabolic rate rose to 7.5 per

* Case histories of nine patients were given when the paper was read. Only three are printed in CALIFORNIA AND WESTERN MEDICINE; others will appear in the reprints.

cent plus. Because she began to have insulin reactions and some gastric symptoms, medication was stopped for a time, but was later resumed in limited doses. At this time the glucose tolerance curve was flat (blood sugar: fasting, 81; one-half hour 129; one hour 84; two hours 77 milligrams per cent). The following year, despite continued treatment with insulin, anterior pituitary substance, ovarian extract, and thyroid extract, the patient began to fail in health and to lose weight. Fourteen months later (February, 1931), her basal metabolic rate had dropped to 37.3 per cent minus, and her weight had decreased to 61¾ pounds (28 kilograms). Injections of theelin were given, but the downhill progress continued. She was seen last at the University of California clinic on September 10, 1931, her weight at that time being 59¼ pounds (26.8 kilograms). Dr. Richard E. Graun of Los Gatos later informed us that she had died in August, 1933. During the last two years of life her course had continued downhill, despite general supportive measures. When seen on the day of her death, she was comatose and very emaciated, and weighed "not more than 50 pounds" (22.7 kilograms); her pulse rate was 44, and the blood pressure was 58 millimeters of mercury systolic, with no definite diastolic level. Permission for an autopsy, unfortunately, was refused.

* * *

CASE 2.*—L. B. (73089M), a 17-year-old, American schoolgirl was admitted to the University of California Hospital on September 11, 1933, with complaints of loss of weight, amenorrhea, and increased growth of hair.

One brother and a cousin were Mongolian idiots. In the past the patient had had only measles. Menarche had occurred at the age of eleven years, and her menstrual periods were regular until the beginning of her present illness. At the time of onset of symptoms her weight was 127 pounds (57.7 kilograms).

Six years before admission to the hospital the patient had had a severe febrile illness, accompanied by an extraocular paresis. During the three weeks of illness she lost 25 pounds (11.3 kilograms) in weight. She then developed anorexia and constipation, and continued to lose weight. Amenorrhea had been present from that time. Four years before entry a downy growth of hair appeared on the face, neck, and back. Two years later she had attacks of acute lower abdominal pain, for which appendectomy was performed without relief resulting. For six months prior to entry she had noted intolerance to cold, slight asthenia, and occasional edema of the ankles in the evening. Basal metabolic rates determined six months before entry were minus 32 per cent and minus 29 per cent. Treatment with various drugs, including thyroid substance, ovarian extract, theelin, and insulin, was of no benefit. Her total loss of weight was 53 pounds (24.0 kilograms).

*Physical Examination.*—The patient's height was 67¾ inches (172 centimeters); her weight, 74 pounds (33.6 kilograms)—ideal weight, 137 pounds (62.3 kilograms). The pulse rate was 40 per minute, and the temperature 34 degrees centigrade. She appeared cachectic, and her skin was dry. A growth of downy hair was visible on the face, back, and extremities. The pubic hair showed normal distribution. The heart was small. The blood pressure was 90 millimeters of mercury systolic; 70 diastolic. A pelvic examination performed by Dr. Charles Hayden showed the uterus to be small, and the external genitalia infantile. The extremities were cold and cyanotic, and there was slight edema of the ankles.

*Laboratory Examinations.*—Blood: hemoglobin, 78 per cent (10.8 grams) (Sahli); red blood cells 3,900,000 per cubic millimeter; white blood cells 9,100 per cubic millimeter, with a normal differential count including one per cent eosinophils. Basal metabolic rate: 47 per cent minus. Glucose tolerance test: blood sugar (fasting), 76; one-half hour 66; one hour 90; two hours 74 milligrams per cent. Whole blood cholesterol, 149 milligrams per cent. Serum calcium, 11.9 milligrams per cent; phosphorus, 3.1 milligrams per cent. Plasma chlorids, 529 milligrams per cent. In the electrocardiogram the complexes were small in all leads. In the roentgenological examination the sella turcica was seen to be normal. Pyelograms showed the kidneys to be normal in size and shape. The bone age was over eighteen years. No abnormalities were observed in the chest, except for a small heart.

*Course and Treatment.*—The progressive loss of weight continued, despite a daily intake of 1,200 to 2,300 calories. Administration of thyroid extract for ten days, followed by injections of Antuitrin S for eleven days, did not improve the patient's condition. During the fourth week she suddenly became very weak and the edema of the ankles increased. The visual fields, which had been normal, showed marked concentric contraction. She finally lapsed into coma and died, despite the use of stimulants, fluids injected intravenously, and large amounts of adrenal-cortical extract (Eschatin) on the day of her death. The last weight determined was 62 pounds (28.2 kilograms).

*Postmortem examination* showed the presence of a chromophobe hyperplasia of the anterior pituitary, atrophy of the adrenal cortex, immature ovaries, and some terminal bronchopneumonia. The viscera were small.

* * *

CASE 3.—P. P. (U 12003), a 17-year-old, white American schoolgirl, was admitted to the University of California Hospital (service of Dr. Francis Scott Smyth and Dr. Howard Naffziger) on April 1, 1937. Her complaints were loss of weight, amenorrhea, and easy fatiguability.

One cousin had died of tuberculosis, and a maternal grandmother of carcinoma. The patient had had the usual childhood diseases. Menarche had occurred at the age of twelve, and her periods had been fairly regular and normal until onset of her present illness. Her average weight had been 125 to 130 pounds (56.8 to 59.0 kilograms) during the year before her illness began.

Ten months before entry into the hospital the patient had had some anorexia, and had begun to lose weight. After a two-month interval, she had a normal menstrual period; and then complete amenorrhea. She was troubled also by sensitivity to cold, constipation, and some irritability and easy weeping. Six months before entry, a basal metabolic rate was found to be minus 40 per cent; and the administration of thyroid substance was started which the patient was still taking at the time of entry. The metabolic rate increased to as high as 5 per cent plus, but she felt no better and continued to lose weight. Her weight at onset of illness had been 130 pounds (59.0 kilograms); and she lost a total of 40 pounds (18.2 kilograms). She had some loss of axillary and pubic hair. Asthenia developed gradually, and finally she had to stop school.

*Physical Examination.*—The patient's height was 64½ inches (164 centimeters); her weight, 89.7 pounds (40.8 kilograms)—ideal weight, 125 pounds (56.8 kilograms). Her pulse rate was 56 per minute, her temperature 36.4 degrees centigrade. She was very thin; her movements and speech were rather slow. The skin was dry, with slight pigmentation over the abdomen (probably due to ultraviolet light treatments). The hair was normal in texture, scant in the axillae, and slightly thinned in the pubic region. The teeth were in good condition. The breasts were fairly well developed. The heart was small. Blood pressure was 94 millimeters of mercury systolic and 60 diastolic; it decreased to 74 millimeters of mercury systolic and 58 diastolic, when she was raised from a prone to a standing position (postural hypotension—Schellong-Strisower reaction). The viscera were small. Pelvic examination by Dr. Alice Maxwell showed that the uterus was normal in size, and the left ovary cystic. The extremities were cold.

*Laboratory Examinations.*—Blood: hemoglobin, 92 per cent (13.2 grams) (Sahli); red blood cells 4,700,000 per cubic millimeter; white blood cells 6,800 per cubic millimeter, with normal differential count, including 2 per cent eosinophils. Basal metabolic rate: 24 per cent minus (the patient still taking thyroid). Glucose tolerance test (1.75 gram per kilogram): fasting, 53.8; one-half hour 108.5; one hour 127.8; two hours 97; three hours 71.6; four hours 60; five hours 105.2; six hours 100.1 milligrams per cent. Nonprotein nitrogen: 42.2 milligrams per cent. Blood urea nitrogen, 22.8 milligrams per cent. Creatinin, 1.8 milligrams per cent. Whole blood chlorids, 351 milligrams per cent (as NaCl). Plasma chlorids (later), 544 milligrams per cent (as NaCl). Serum calcium, 9.8 milligrams per cent. Phosphorus, 6.68 milligrams per cent. Visual fields normal. Gastric analysis (fasting specimen only), no free HCl; total acidity not over two units. Tuberculin tests, negative. Roentgenological examination showed the sella

* This case, with discussion of pathologic findings, will be reported more fully in a later paper.

turcica to be normal; the bone age was seventeen to eighteen years; the lungs were clear; the heart small.

*Course and Treatment.*—The patient was started on daily injections of whole pituitary extract (Armour), but these did not have any appreciable effect. She was then started on Polyansyn, and discharged from the hospital. However, the regimen was not well followed at home, and she was finally readmitted with the general condition definitely worse. She was then started on a regimen of Polyansyn and insulin together, but after two weeks of this she became disoriented and depressed and refused to eat. The therapy was stopped and psychotherapy begun, under which she gradually cleared and began to take food satisfactorily. This resulted in a gain in weight of 25 pounds (11.4 kilograms) in seven weeks, and on discharge the patient weighed 104.7 pounds (47.6 kilograms). Her response to psychotherapy and increased intake of food would suggest that the primary diagnosis here should have been anorexia nervosa, rather than Simmonds' disease. This case is an excellent example of the occasional difficulty experienced in differentiating these two conditions clinically.

## DIAGNOSIS

All of the patients whose histories are given above manifested the cardinal findings of Simmonds' disease as noted in the introductory paragraphs of this paper. Each had had considerable loss of weight, the least being 22.5 pounds (10.2 kilograms) (Case 7) and the most, 53 pounds (24.0 kilograms) (Case 2); the average loss of weight was 35.6 pounds (16.1 kilograms). At least five patients (Cases 1, 2, 3, 4, and 5) showed definite emaciation, being, respectively, 64¼ pounds (29.2 kilograms), 63 pounds (28.7 kilograms), 35 pounds (15.9 kilograms), 43 pounds (19.5 kilograms), and 51 pounds (23.2 kilograms) under their ideal weights. One of the female patients in whom the onset had occurred at puberty had never menstruated; while amenorrhea lasting from ten months to seventeen years was experienced by each of the others. The basal metabolic rates of all the patients were low, varying from minus 18 per cent to minus 47 per cent and averaging 32.1 per cent minus.

Concerning the less constant characteristics: All but one of the patients were females. Onset of illness occurred at or shortly after puberty in three patients; early in the second decade of life in four; in the third decade in one; and at the beginning of the fourth decade in one (the male patient, Case 7). The latest onset among the female patients (Case 6) followed a fifth pregnancy which had been attended by severe complications. At the time of examination the duration of the disease had been from ten months to seventeen years. All of the patients complained of asthenia, and three specifically of loss of libido although this symptom was not always ascertained in the unmarried patients. Seven patients had noted intolerance to cold. In regard to psychic changes, four patients had experienced decided slowing of mental processes (Cases 4, 5, 6, and 7); three had had a feeling of depression (Cases 3, 5, and 9); and one (Case 6) had at one time been apathetic to the extent of suggesting a diagnosis of "dementia praecox." Gastro-intestinal symptoms were of common occurrence, and were specific complaints of seven of the patients. Slight transient diabetes insipidus was present in one instance (Case 9). Anorexia, which was a frequent symptom, undoubtedly contributed to the continued loss of weight, but was not considered to be the primary cause. However, it is of interest to note that the subsequent course of Case 3, with a continued gain in weight under psychotherapy and increased intake of food, caused us to doubt the diagnosis and eventually classify the patient as a case of anorexia nervosa.

Of the physical findings, dry skin was noted in eight of the patients, but scanty axillary and pubic hair was noted in only three. Four patients had dental caries, and all had hypotension (the limits were 80 to 100 millimeters of mercury systolic and 50 to 70 diastolic). In the female patients the internal genitalia were small in six instances, and in one patient (Case 1) the cervix was absent. The one male patient showed slight genital atrophy.

The laboratory findings were of some interest. In the glucose tolerance studies, definitely flat curves were found at some time in seven patients, while two (Cases 1 and 5) had curves of the diabetic type; however, one of the latter was transient. In Cases 7 and 9 there were definite symptoms of hypoglycemia. Three patients were tested for specific dynamic reaction to food, which was found to be diminished in two. A mild secondary anemia was present in three cases, and a slight eosinophilia in one. The blood cholesterol was normal in four cases, and elevated in two. In sevent patients the sella turcica was normal, and it was small and shallow in one (Case 1, onset aet. 15).

Therefore, in our series, loss of weight, amenorrhea in females and loss of libido in the male patient, and lowered basal metabolic rates, were constant findings; the other characteristics were more or less variable.

## TREATMENT

Since it is accepted that the pathologic physiology of Simmonds' disease is related to failure of the anterior pituitary, the logical treatment would seem to be therapy by replacement with anterior pituitary extract. For some of our recent cases an extract prepared by Professor J. B. Collip of Montreal (polyansyn) and kindly furnished to us by Ayerst, McKenna and Harrison, has been used. Administration of this extract caused some subjective improvement in general well-being, and appetite, and decrease of mental sluggishness; but except in one patient (Case 6), it did not result in a marked gain of weight. The symptoms of amenorrhea and lack of libido were not affected. Insulin therapy improved the condition of one patient (Case 1) temporarily, and caused a definite gain in two others (Cases 5 and 7). However, it must be administered with caution in this disease because of the frequent tendency to hypoglycemia. It is interesting to note that in Case 5, Polyansyn was necessary in addition to the insulin in order to cause continued gain in weight. Thyroid medication gave temporary benefit to one patient (Case 6) early in the course of the disease, but later was poorly tolerated. Five other patients who were treated with thyroid substance reacted unfavorably. This form of therapy seemed to hasten loss of weight, and to cause increased nervousness. Daily injections of Follutein gave temporary benefit to one patient early in the disease.

It is felt that preparations of anterior pituitary should be tried in adequate amounts and for long periods of time. Further observation of our patients is considered necessary before we can definitely accept the preparations available at present as being specifically beneficial.

## SUMMARY

Nine cases are presented in which the history and findings were suggestive of Simmonds' disease. The classical and most constant findings are loss of weight, loss of sexual function, and lowered basal metabolic rate. The authors feel that this disease should be considered when a patient presents continued loss of weight for which no other cause can be found. Clinical differentiation from anorexia nervosa is occasionally very difficult, and the subsequent course of one of our cases caused it to be placed in this category.

Treatment is discussed; and, although therapy by replacement with anterior pituitary extract seems logical, its administration has thus far, at least in our experience, been somewhat disappointing. More potent preparations are needed. Despite the low basal metabolic rates found in these patients, administration of thyroid substance is ineffectual. A fattening regimen, with the use of insulin, may be tried cautiously.

The condition of some patients may improve spontaneously, but the eventual prognosis is usually grave.

384 Post Street.

## REFERENCES

1. Simmonds. M.: Ueber Hypophysisschwund mit tödlichem Ausgang, Deutsche. med. Wchnschr., 40:322, 1914.
2. Silver, S.: Simmonds' Disease, Arch. Int. Med., 51:175 (Feb.), 1933.

## DISCUSSION

C. Kelly Canelo, M.D. (Medico-Dental Building, San Jose).—Simmonds' disease is a condition of extreme debility and cachexia, caused by lack of function of the anterior lobe of the pituitary.

The most common etiological factor is an obstruction to the blood supply resulting from an embolus. Tumors, cysts and inflammatory processes of the pituitary itself are frequent. It is not uncommon to find a history of frequent pregnancies and then a delivery complicated by hemorrhage and infection. Howard reports a case of Simmond's disease, proved at autopsy, in a woman of twenty-three years, due to a tumor of Rathke's pouch, producing pressure on the pituitary.

The cardinal symptoms of this disease are: (1) Loss of weight and strength; (2) Loss of sex function; (3) Low basal metabolic rate. Weight loss is often as much as 65 per cent of the original weight of the patient. Brattan reported a case in a woman who died nine months after a long series of pregnancies; autopsy showed all the usual findings of Simmond's disease, except that there was no weight loss.

Loss of sex function includes amenorrhea and loss of libido and potentia.

The basal metabolic rate is frequently from 30 to 40 per cent below the calculated normal rate.

Other findings usually present are: dry, pallid skin, falling of the hair and teeth, senile atrophy of the lower jaw, decalcification of the bones, hypotension, subnormal temperature, bradycardia, splanchnomicria, low-fasting blood sugar and loss of specific dynamic reaction to protein, carbohydrate, and fat.

In making a diagnosis of Simmonds' disease, one must not be caught in the "endocrine whirl," but must rule out all other debilitating diseases. Anorexia nervosa mimics Simmond's disease and requires competent psychiatric observation to rule out this possibility. In the absence of pituitary signs, cancer must be thought of and diligently searched for. Addison's disease most usually shows pigmentation especially of the mucous membranes, and in this condition wasting is not the usual finding.

In spite of basal metabolic rates of minus 30 to 40 per cent, thyroid extract does not benefit these patients even though their metabolic rate be brought up to normal by means of thyroid.

This series of cases, although carefully controlled and treated with a reliable anterior pituitary preparation, has failed to show the complete response that might be desired.

Turner, however, reports a case of Simmonds' disease which responded quite promptly and completely with a similar anterior pituitary preparation.

Hawkinson, in 1935, reported one case that responded satisfactorily to A. P. L.

Herman reported, in the German literature in 1934, the good results he obtained in three cases by the use of prolan.

Barr reports one case that showed marked improvement with storage of calcium, phosphorus and nitrogen on no specific treatment, but adequate and attractive diet, rest, and good nursing care; it is possible that this was a case of transient Simmonds' disease due to mere suppression of the anterior lobe of the pituitary, or it may have been a case of anorexia nervosa.

Kylin reports a series of twenty-three cases treated by implantation of calves' hypophyses. Of these patients, three had been under observation only a short time at the time of his report; of the other twenty, eighteen showed good results.

Steinitz, in 1932, gave a report of six cases. He treated his cases at first with pituitary preparations alone and found that he was able to correct the trophic changes, but the weight loss either progressed or remained unimproved. In spite of low-fasting blood sugars, he found that the glucose tolerance curves suggested a lack of insulin; accordingly, he added insulin to his treatment and achieved a satisfactory response in his patients.

In the majority of patients this latter method of treatment would seem to be the most satisfactory at the present time.

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Lewis T. Bullock, M.D. (1136 West Sixth Street, Los Angeles).—There are many problems concerning Simmonds' disease that remain unanswered. In theory, at least, it is due to a lack of all of the secretions of the anterior pituitary gland. It is safe to say that we will not entirely understand this syndrome until we know all of the essential aspects of the physiology of the pituitary, and that day is still for the future. A case of pituitary cachexia, however, provides the inquisitive physician with a remarkable opportunity to study in man the disturbances produced by the absence of pituitary secretions, and it may be that important physiological data will be developed from this source.

The essential problem of why these patients lose weight and die is not entirely clear. Though necessary for normal growth in stature, it has not been proved that the lack of growth hormone is alone responsible for the loss of weight. Even if this were true the mechanism is not understood. Is it a lack of appetite and food intake, a lack of absorption, or a lack of utilization of absorbed food elements? I had the pleasure of observing one of the autopsied patients in this series, who lost weight in spite of an increased and adequate consumption of food. The flat glucose tolerance curve and absence of specific dynamic action of protein raise the question of inadequate absorption. If it is from a lack of utilization of absorbed material, the metabolic changes responsible for this require clarification. The lack of thyrotropic hormone would not explain the loss of weight or death and deleterious results which have followed its administration. It does not seem probable that the gonadotropic hormones are important in maintaining weight, and life and improvement reported in the literature from the use of these substances seem questionable. Hypoglycemia is often present, but there is no proof that this is the usual cause of death. Adrenal insufficiency is a possible cause of the terminal coma and death, but this has not been confirmed by experience. In the absence of more detailed knowledge concerning the mechanism of the loss of weight and the cause of death, it is obvious that treatment must be unsatisfactory.

The clinical aspects of this syndrome have been well reviewed, and the characteristic picture should be in the diagnostic armamentarium of every physician. I should

like to add the loss of pubic hair to the list of cardinal findings. This change was present in thirty-five of Silver's forty-one autopsied and proved cases. Doctors Escamilla and Lisser have wisely emphasized that the other findings of cachexia, amenorrhea, and low basal metabolism can be exactly duplicated by anorexia nervosa. I have seen a similar case of a patient completely cured by psychotherapy alone. This important finding which distinguishes Simmonds' disease from anorexia nervosa is absent in almost all of the cases reported in the literature as having been cured by various injections or transplants. No claim for cure can be accepted as conclusive when this is absent. The characteristic remissions with a prolonged course of the disease, up to forty-four years in proved cases, must also be considered in relation to therapeutic triumphs.

I wish to congratulate Doctors Escamilla and Lisser on their excellent report of the clinical aspects of this syndrome, and most particularly upon their sound, careful and conservative approach to the problem of therapy. It is by studies of this type, with careful observations of the results obtained from available preparations, that we may finally arrive at a preparation capable of replacing the essential secretions of the anterior pituitary that are lacking in Simmonds' disease.

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Doctor Escamilla (Closing).—I wish to thank Doctor Canelo and Doctor Bullock for their discussions, which have contributed substantially to a more complete consideration of Simmonds' disease. Doctor Canelo has added data concerning the types of treatment utilized for this disease. Doctor Bullock has stressed our inability at present to explain adequately some of the characteristics of the disease. He has added the interesting suggestion that loss of pubic hair should be included in the list of cardinal signs. It is true that a recent review of the literature has revealed more or less thinning or loss of axillary and pubic hair in 81 per cent of sixty-nine autopsied cases. This is essentially the sexual hair, and may be related to lack of the gonadotropic fraction from the anterior pituitary. However, it is frequently a late development and is most marked in the far-advanced or very severe cases. It seems safe to state that the clinical diagnosis can frequently be made with reasonable certainty, even if there has been little or no thinning of axillary or pubic hair, and therefore, in our opinion, its inclusion as a cardinal or essential finding does not seem justified. Indeed, the patient which Doctor Bullock observed (Case 2 in the paper), who died and was found to have pituitary pathology, had abundant pubic and axillary hair, yet in every other respect was a most typical example of Simmonds' disease. It is of interest to note that since this paper was presented communications have been received from colleagues in several parts of the state, describing cases which apparently can be classified as Simmonds' disease. This seems a further confirmation of the suggestion that the disease is more common than heretofore suspected.

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## MONOCYTIC LEUKEMIA: SOME BLOOD AND BONE-MARROW STUDIES*

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CASES of monocytic leukemia, so far studied by the author, have exemplified the necessity of careful identification of both mature and primitive monocytes in the blood. Observations require repeated verification. This is the more true because of the close similarity of the clinical picture to that of other types of acute leukemia.

The sudden, although transient appearance of considerable numbers of myelocytes in the blood during the course of monocytic leukemia, and the occasional finding of noticeable numbers of cells closely like or identical in morphology with mature and primitive monocytes in the blood of cases of acute myeloblastic leukemia suggest a close relationship of these cell types.

### TWO TYPES OF BLOOD PICTURE

In general there are two types of blood picture in monocytic leukemia:

1. The one occurs most often in patients whose condition tends to be less acute and who have short periods of slight improvement, suggesting remissions. In these cases the blood picture may show an inclination to become partially myeloblastic and myelocytic as a terminal event. It appears to be due to the occurrence of this type of case that controversy as to the existence of monocytic leukemia as a separate form so long existed. In this type the total white count is either within normal limits or is already moderately elevated when the patient is first seen. The count may show considerable day-to-day variation, but shows a general tendency to rise as the disease progresses. The platelet count also varies, but usually remains definitely subnormal and progresses to a low level, accompanied by a lengthened bleeding time. While the neutrophils are reduced in percentage, the absolute number remains, for the most part, above the lower limit of normal, and rises with the increase in the total leukocyte count. Lymphocytes also usually increase in absolute numbers with the leukocyte increase.

It is important to note that in one patient who was classed within this group, and in which the myelocytic cells reached 19 per cent of 258,000 leukocytes per cubic millimeter, the monocytic cells were still 51 per cent of all the leukocytes. This was observed during the last few days of life. Two days before death, the monocytic cells were 59 per cent of the leukocytes.

2. With the other type of blood picture some patients show a neutrophilic leukopenia when first seen, although there is a simultaneous left nuclear shift. Progression to transient, complete agranulocytosis, with low total leukocyte count, may occur. The red cell count, hemoglobin content of the blood and platelet count, may still remain comparatively undisturbed at the earlier observations, so that the diagnosis rests largely upon recognition of the monocytic picture. This tendency to agranulocytosis is evident not only during leukopenic phases, but persisted in one patient studied at a time when the total leukocyte count was as high as 130,000 per cubic millimeters.

It is further significant that in this second type of blood picture, primitive myeloid cells are absent from the blood throughout the entire course of the disease, or appear in less conspicuous numbers than ordinarily seen in neutrophilic leukocytosis with a similarly pronounced left nuclear shift.

Relative to this second type in which the more acute cases of monocytic leukemia appear to fall, there can be no question of confusion with myeloblastic leukemia.

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